# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>15270C-3-1PC | **FOR FURTHER ACTION** | See item 4 below |
| International application No.<br>PCT/US2008/060926 | International filing date *(day/month/year)*<br>18 April 2008 (18.04.2008) | Priority date *(day/month/year)*<br>18 April 2007 (18.04.2007) |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 | | |
| Applicant<br>JANSSEN ALZHEIMER IMMUNOTHERAPY | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☒ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

| | |
|---|---|
| | Date of issuance of this report<br>20 October 2009 (20.10.2009) |
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No. +41 22 338 82 70 | Authorized officer<br>Beate Giffo-Schmitt<br>e-mail: pt03.pct@wipo.int |

Form PCT/IB/373 (January 2004)

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ROSEMARIE L. CELLI
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SAN FRANCISCO, CA 94111-3834

# PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 09 OCT 2008 |
| Applicant's or agent's file reference<br>15270C-3-1PC | FOR FURTHER ACTION<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US 08/60926 | 18 April 2008 (18.04.2008) | 18 April 2007 (18.04.2007) |

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 39/00; G01N 33/53; C07K 16/00 (2008.04)
USPC - 530/388.1; 536/23.53

Applicant ELAN PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/US | Date of completion of this opinion | Authorized officer: |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | 03 Oct 2008 (03.10.2008) | Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/60926

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

Group I: claims 1-30 and 69-106, drawn to a method of treating cerebral amyloid angiopathy (CAA) or of affecting prophylaxis against CAA comprising: administration of an antibody specific for the N-terminus of Abeta or a fragment of Abeta that will induce such an antibody.

Group II: claims 31 and 48-63, drawn to the use of an antibody specific for the N-terminus of Abeta or a fragment of Abeta that will induce such an antibody for the treatment or prophylaxis of Alzheimer's disease; and methods of treating Alzheimer's disease comprising: administration of an antibody specific for the N-terminus of Abeta or a fragment of Abeta that will induce such an antibody.

Group III: claims 32-47, drawn to a method for reducing vascular amyloid by administration of an antibody specific for the N-terminus of Abeta.

Group IV: claim 64-68, drawn to a kit for treatment of cerebral amyloid angiopathy (CAA) comprising: a glass vial containing a formulation and a set of instructions.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature.

The special technical feature of Groups I-IV is the use of either (1) an antibody which is specific for the N-terminal 7 amino acids of the A-beta peptide or (2) a fragment of the N-terminus of the A-beta peptide which induces such an antibody, for the treatment of diseases characterized by aberrant deposition of amyloid proteins (CAA, Alzheimer's, vascular amyloid). The special technical feature of Groups I-IV does not represent an improvement over the prior art of Rosenthal et al. (US 2006/0057701 A1) which teaches the use of antibodies specific for the N-terminus of A-beta for the treatment of diseases characterized by deposition of amyloid proteins (para [0009]-[0016] and [0078]-[0080]) or Schenk (US 6,787,637 B1) which teaches the use of antibodies specific for the N-terminal 7 amino acids of Abeta in treating diseases associated with amyloid deposits (col 2, ln 22-52). According to PCT Rule 13.2, unity of invention exists only when the same or corresponding special technical feature is shared by all claimed inventions.

In this case, the first named invention and first named species that will be searched without additional fees is Group I represented by claims 1-30 and 69-106.

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts
   - ☒ the parts relating to claims Nos. 1-30 and 69-106

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 15-26, 28, and 69-106 | YES |
| | Claims | 1-14, 27, 29, and 30 | NO |
| Inventive step (IS) | Claims | None | YES |
| | Claims | 1-30 and 69-106 | NO |
| Industrial applicability (IA) | Claims | 1-30 and 69-106 | YES |
| | Claims | None | NO |

2. Citations and explanations:

Claims 1-4, 7-14, 27, 29, and 30 lack novelty under PCT Article 33(2) as being anticipated by US 2002/0094335 A1 to Chalifour et al. (hereinafter "Chalifour").

As per claim 1, Chalifour teaches a method of treating CAA, comprising
-- administering to a patient having or suspected of having CAA (amyloid related disease such as Cerebral Amyloid Angiopathy; para [0017]; [0019]; [0027]) an effective regime of an agent,
-- wherein the agent is an antibody (passive immunization by administering an antibody; para [0037]) that is specific for the N-terminus of Abeta (antibodies against N-terminus of Abeta- Immunogenic fragment comprises the N-terminus, such as Abeta 1-5; para [0068]; [0126]) or induces such an antibody after administration to the patient (antigenic amount of an all-D peptide which elicits production of antibodies such as Abeta(1-7) all-D; para [0026]; [0174]) and thereby treating the patient (para [0017]).

As per claim 2, Chalifour teaches the method of claim 1, wherein the agent is an antibody (passive immunization by administering an antibody; para [0037]).

As per claim 3, Chalifour teaches the method of claim 2, wherein the agent is an antibody that binds within residues 1-5 of Abeta (Immunogenic fragment comprises Abeta 1-5; para [0126]).

As per claim 4, Chalifour teaches the method of claim 2, wherein the antibody is a humanized, human, or chimeric antibody (para [0069).

As per claim 7, Chalifour teaches the method of claim 1, wherein the agent is a fragment of Abeta (antigenic amount of an all-D peptide which elicits production of antibodies. such as Abeta(1-7) all-D; para [0026]; [0174]).

As per claim 8, Chalifour teaches the method of claim 7, wherein the fragment begins at residue 1 of Abeta and ends at one of residues 5-10 of Abeta (antigenic amount of an all-D peptide which elicits production of antibodies. such as Abeta(1-7) all-D; para [0026]; [0174]).

As per claim 9, Chalifour teaches the method of claim 7, wherein the fragment is Abeta 1-7 (antigenic amount of an all-D peptide which elicits production of antibodies. such as Abeta(1-7) all-D; para [0026]; [0174]).

As per claim 10, Chalifour teaches the method of claim 7, wherein the fragment of Abeta is administered with a pharmaceutically acceptable adjuvant (para [0022]).

As per claim 11, Chalifour teaches the method of claim 7, wherein the fragment of Abeta is linked to a carrier that helps the fragment induce antibodies to the fragment (carrier protein, such as keyhole limpet hemocyanin, Cd3 or tetanus toxin; para [0022]).

As per claim 12, Chalifour teaches the method of claim 11, wherein the carrier is linked to the C-terminus of the fragment (therapeutic epitope comprising a "free N-terminal residue" of A.beta; para [0137]).

As per claims 13 and 14, Chalifour teaches the method of claim 1, further comprising determining that a patient has CAA, wherein the determining step occurs before the administration step, as recited by claim 13, and wherein the determining step determines that a patient is suffering from a clinical symptom of CAA, as recited by claim 14 (patients currently showing symptoms of disease; para [0069]).

As per claim 27, Chalifour teaches the method of claim 1, wherein the antibody is administered intravenously or subcutaneously (para [0037]).

As per claim 29, Chalifour teaches the method of claim 1, further comprising administering a second agent effective to treat CAA (an additional anti-amyloid treatment regimen; para [0019]; [0146]).

**********continued in supplemental box**********

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
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**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V No 2 (citations and explanations)

As per claim 30, Chalifour teaches a method of effecting prophylaxis (prevention; para [0017]) against CAA, comprising
-- administering to a patient susceptible to CAA (amyloid related disease such as Cerebral Amyloid Angiopathy; para [0017]; [0019]; [0027]) an effective regime of an agent,
-- wherein the agent is an antibody that is specific for the N-terminus (antibodies against N-terminus of Abeta-Immunogenic fragment comprises the N-terminus, such as Abeta 1-5; para [0068]; [0126]) or induces such an antibody after administration to the patient and thereby effecting prophylaxis of the patient (antigenic amount of an all-D peptide which elicits production of antibodiesL such as Abeta(1-7) all-D; para [0026]; [0174]) and thereby treating the patient (para [0017]).

Claims 1, 2, and 4-6 lack novelty under PCT Article 33(2) as being anticipated by US 2007/0021454 A1 (Coburn).

As per claims 1 and 2, Coburn teaches a method of treating CAA, comprising administering to a patient having or suspected of having CAA (compound of the invention is administered to treat a disease mediated by abnormal cleavage of amyloid precursor protein, such as cerebral amyloid angiopathy; para [0445]) an effective regime of an agent, wherein the agent is an antibody that is specific for the N-terminus of Abeta (compound of the invention is combined with bapineuzumab; para [0448]) and thereby treating the patient.

As per claims 4-6, as discussed above, Coburn teaches the humanized 3D6 antibody, bapineuzumab (para [0448]).

Claims 15, 16, 18-26, 28 and 69-106 lack an inventive step under PCT Article 33(3) as being obvious over Chalifour, as above, in view of US 6,787,637 B1 (Schenk).

As per claim 15, Chalifour teaches the method of claim 1, as discussed above. Chalifour teaches that either CAA or Alzheimer's disease may be treated by the method (para [0017]; [0054]; [0055]) but teaches distinctions of the two diseases, including differences in the plaques (fibrils) that characterize the disease (para [0054]; [0055]; [0093]; [0099]; [0103] and Table 1). Although Chalifour does not explicitly teach wherein the patient lacks plaques characteristic of Alzheimer's disease in the brain, a skilled artisan would have found such a patient further obvious to obtain the invention as claimed because Chalifour teaches treating CAA or Alzheimer's in distinct embodiments (para [0054]; [0055]) and teaches the differences in plaques that characterize respective disease para [0054]; [0055]; [0093]; [0099]; [0103] and Table 1) and a skilled artisan would have appreciated that a patient without Alzheimer's disease would not have the plaques that characterize the disease.

As per claim 16, it is further obvious because a skilled artisan would have readily appreciated that a skilled artisan would have appreciated that a patient CAA and without Alzheimer's disease would not show the symptoms of Alzheimer's disease.

As per claim 18, Chalifour teaches the method of claim 1, as discussed above. Chalifour teaches administering the antibody at a dosage of 0.0001 to 100 mg/kg (para [0070]) but does not teach wherein the dosage of the antibody is between about 0.01 to about 5 mg/kg.
However, Schenk also teaches treating a disease associated with amyloid deposits of A.beta (although CAA is not specifically taught) by administering an antibody that is specific for the N-terminus of Abeta (col 2, ln 21-51) and further teaches administering the antibody at a dosage of between about 0.01 to about 5 mg/kg (col 27, ln 4-6).
One skilled in the art at the time the invention was made would have found obvious the methd of Chalifour, wherein the dosage of the antibody is between about 0.01 to about 5 mg/kg, as taught by Schenk, to obtain the invention as claimed in order to provide an effective dosage because both Chalifour and Schenk teach administering an antibody specific for the N-terminus of Abeta to treat a disease associated with amyloid deposits of A.beta.

As per claim 19, Schenk teaches wherein the dosage of the antibody is between about 0.1 to about 5 mg/kg (col 27, ln 6-8).

As per claims 20 and 21, although the claimed dose ranges are not specifically taught, one skilled in the art would have found said ranges obvious to obtain the invention as claimed based on routine experimentation since Schenk teaches the antibody is administered at a dosage that encompasses the claimed dosage, between about 0.01 to 5 mg/kg (col 27, ln 4-6).

As per claim 22, Schenk teaches wherein the dosage is between about 0.5 to about 3 mg/kg (col 27, ln 6-8).
As per claim 23, Schenk teaches wherein the dosage is between about 0.5 to about 1.5 mg/kg (col 27, ln 6-8).
As per claim 24, Schenk teaches wherein the dosage is administered on multiple occasions (col 27, ln 7-15).
As per claim 25, Schenk teaches dosage is administered is weekly to quarterly (col 27, ln 7-15).

As per claim 26, although a dosage administration of every 13 weeks is not specifically taught, one skilled in the art would have found said administration obvious to obtain the invention as claimed based on routine experimentation since Schenk teaches the antibody is administered 3-6 months (col 27, ln 7-10).

As per claim 28, although Chalifour does not explicitly teach monitoring for changes in signs or symptoms of CAA responsive to the administrating step, a skilled artisan would have found it obvious to monitor for changes in symptoms of CAA to obtain the invention as claimed because it is well known in the art to monitor for changes in symptoms after treating a disease in order to confirm a successful treatment and because Chalifour explicitly teaches treating CAA (para [0017]; [0055]) and treating symptomatic patients (para [0069]).

**********continued in next supplemental box**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/60926

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V(2) (citations and explanations) and the preceding Supplemental Box:

As per claim 69, Chalifour teaches the method of claim 2, as discussed above. Chalifour teaches administering the antibody at a dosage of 0.0001 to 100 mg/kg (para [0070]) but does not teach wherein the antibody is administered in a regime sufficient to maintain an average serum concentration of the antibody in the patient in a range of 1-15 ug antibody/ml serum.
However, Schenk also teaches treating a disease associated with amyloid deposits of A.beta (although CAA is not specifically taught) by administering an antibody that is specific for the N-terminus of Abeta (col 2, ln 21-51) and further teaches administering the antibody in a regime sufficient to maintain an average serum concentration of the antibody in the patient in a range of 1-100 ug antibody/ml plasma (col 27, ln 17-19).
One skilled in the art at the time the invention was made would have found obvious the methd of Chalifour, wherein the antibody is administered in a regime sufficient to maintain an average serum concentration of the antibody in the patient in a range of 1-15 ug antibody/ml serum, as suggested by Schenk, to obtain the invention as claimed because both Chalifour and Schenk teach administering an antibody specific for the N-terminus of Abeta to treat a disease associated with amyloid deposits of A.beta. Although the specific range of 1-15ug/ml serum is not specifically taught, a skilled artisan would have found the claimed range obvious based on routine experimentation since Schenk teaches a range of 1-100 ug antibody/ml plasma (col 27, ln 17-19).

As per claims 70-72, they are further obvious for the reasons discussed in calim 69, specifically because although the specific ranges are not specifically taught, a skilled artisan would have found the claimed range obvious based on routine experimentation since Schenk teaches a range of 1-100 ug antibody/ml plasma (col 27, ln 17-19).

As per claim 73, both Chalifour (para [0037]) and Schenk (col 3, ln 5-8) teach wherein the antibody is administered intravenously.
As per claims 74 and 75, Schenk further teaches wherein a dose of 0.5-1.0 or 0.1-1.0 mg/kg is administered monthly (col 27, ln 6-10).
As per claim 76, both Chalifour (para [0037]) and Schenk (col 3, ln 5-8) teach wherein the antibody is administered subcutaneously.
As per claim 77, Schenk teaches wherein the antibody is administered at a frequency between weekly and monthly (col 27, ln 8-15).
As per claim 78, Schenk teaches wherein the antibody is administered weekly or biweekly (col 27, ln 8-15).

As per claims 79-83, although the claimed dose ranges are not specifically taught, one skilled in the art would have found said ranges obvious to obtain the invention as claimed based on routine experimentation since Schenk teaches the antibody is administered at a dosage that encompasses the claimed dosage, between about 0.01 to 5 mg/kg (col 27, ln 4-6).

As per claims 84 and 85, Schenk teaches weekly or biweekly administrations (col 27, ln 4-15). although the claimed dose ranges are not specifically taught, one skilled in the art would have found said ranges obvious to obtain the invention as claimed based on routine experimentation since Schenk teaches the antibody is administered at a dosage that encompasses the claimed dosage, between about 0.01 to 5 mg/kg (col 27, ln 4-6).

As per claims 86 and 87, although an average serum concentration of the antibody is maintained for at least six months or at least a year is not specifically taught, one skilled in the art would have found such concentrations obvious to obtain the invention as claimed because Schenk teaches administering the antibody once every 3 to 6 months or once a year, depending on the plasma antibody concentration (col 27, ln 7-19).

As per claim 88, although Chalifour does not teach measuring the concentration of antibody in the serum and adjusting the regime if the measured concentration falls outside the range, one skilled in the art would have found such a measurement obvious to obtain the invention as claimed because Schenk teaches that antibody dose intervals can also be irregular as indicated by measuring blood levels of antibody to A.beta in the patient and the dosage can be adjusted to achieve a plasma antibody concentration (col 27, ln 10-19).

As per claim 89, Schenk teaches wherein the antibody is administered at a frequency between weekly and monthly (col 27, ln 8-15). Although the claimed dose range of .01-0.6 mg/kg is not specifically taught, one skilled in the art would have found said ranges obvious to obtain the invention as claimed based on routine experimentation since Schenk teaches the antibody is administered at a dosage that encompasses the claimed dosage, between about 0.01 to 5 mg/kg (col 27, ln 4-6).

As per claims 90 and 91, although the claimed dose ranges are not specifically taught, one skilled in the art would have found said ranges obvious to obtain the invention as claimed based on routine experimentation since Schenk teaches the antibody is administered at a dosage that encompasses the claimed dosage, between about 0.01 to 5 mg/kg (col 27, ln 4-6).

As per claims 92-106, Schenk teaches weekly, biweekly, and monthly administrations (col 27, ln 7-15). Although the claimed dose ranges are not specifically taught, one skilled in the art would have found said ranges obvious to obtain the invention as claimed based on routine experimentation since Schenk teaches the antibody is administered at a dose of between about 0.01 to 5 mg/kg (col 27, ln 4-6).

Claims 17 lacks an inventive step under PCT Article 33(3) as being obvious over Chalifour, as above, in view of the article entitled "Familial cerebral amyloid angiopathy related to stroke and dementia" by Frangione et al. (hereinafter "Frangione").

As per claim 17, Chalifour teaches that treating CAA (para [0017]; [0055]) and treating treating symptomatic patients (para [0069]) but does not teach wherein the patient has had a heart attack or stroke. However, Frangione teaches that CAA associated with stroke (abstract). One skilled in the art at the time the invention was made would have found it obvious to treat a CAA patient that has had a stroke, as suggested by Frangione, in the method of Chalifour to obtain the invention as claimed because a skilled artisan would have appreciated that a symptomatic CAA patient, as taught by Chalifour would have had a stroke since Frangione teaches that CAA associated with stroke.

Claims 1-30 and 69-106 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

1: Amyloid. 2001 Jul;8 Suppl 1:36-42.

# Familial cerebral amyloid angiopathy related to stroke and dementia.

Frangione B, Révész T, Vidal R, Holton J, Lashley T, Houlden H, Wood N, Rostagno A, Plant G, Ghiso J.

Department of Pathology, New York University School of Medicine, New York 10016, USA. frangb01@popmail.med.nyu.edu

The term cerebral amyloid angiopathy (CAA) refers to the specific deposition of amyloid fibrils in the walls of leptomeningeal and cortical arteries, arterioles and, although less frequently in capillaries and veins. It is commonly associated with Alzheimers disease, Down's syndrome and normal aging, as well as with a variety of familial conditions related to stroke and/or dementia: hereditary cerebral hemorrhage with amyloidosis of Icelandic type (HCHWA-I), various inherited disorders linked to Abeta mutants (including the Dutch variant of HCHWA), and the recently described chromosome 13 familial dementia in British and Danish kindreds. This review focuses on four different types of hereditary CAA, emphasizing the notion that CAA is not only related to stroke but also to neurodegeneration and dementia of the Alzheimer's type.

PMID: 11676288 [PubMed - indexed for MEDLINE]